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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/807,221
Filing Date	23 March 2004
First Named Inventor	J.K. MEHRA et al.
Group Art Unit	1712
Examiner Name	
Total Number of Pages in This Submission: 1	Attorney Docket Number: Ipca Labs

ENCLOSURES *(check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment / Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Assignment Papers *(for an Application)*
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
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- ☐ CD, Number of CD(s) _____
- ☐ After Allowance Communication to Group
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
- ☐ Proprietary Information
- ☐ Status Letter
- ☑ Other Enclosure(s) *(please identify below)*:

Certified copy of foreign priority patent applic'n: India Patent Application Serial No. 1185/MUM/2003

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm *or* Individual name	Pharmaceutical Patent Attorneys, LLC 55 Madison Avenue, 4th floor, Morristown NJ 07960-7397 USA
Signature	/9/
Date	see below date

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231 on this date: see below date

Typed or printed name	J. M. Pohl, Reg. No. 35,325		
Signature	/9/	Date	28 Nov 2005

बौध्दिक सम्पदा भारत
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सत्यमेव जयते

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THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of the Patent Application and Provisional Specification filed on 14/11/2003 in respect of Patent Application No.1185/MUM/2003 of **(a) M/S. IPCA LABORATORIES LIMITED, (b) 48, Kandivli Industrial Estate, Mumbai – 400 067, Maharashtra, India (c) Indian company incorporated under the Companies Act 1956.**

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.

CERTIFIED COPY OF PRIORITY DOCUMENT

Dated this 21st day of October 2005

(A.T. PATRE)
ASSTT. CONTROLLER OF PATENTS & DESIGNS.

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT
[See section 5 (2), 7, 54 and 135; rule 39]

1. We,

   (a) M/S. IPCA LABORATORIES LIMITED

   (b) 48, Kandivli Industrial Estate, Mumbai – 400 067, Maharashtra, India

   (c) Indian company incorporated under the Companies Act 1956

2. Hereby declare –

   (a) that we are in possession of an invention titled **"AN IMPROVED INDUSTRIAL PROCESS FOR MANUFACTURE OF METOPROLOL BASE AND SALTS THEREOF"**

   (b) that the Provisional Specification relating to this invention is filed with this application.

   (c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventor(s) for the said invention are

   (a) Mehra Janakraj Karamchand

   (b) IPCA Laboratories Limited
   123-AB, Kandivli Industrial Estate
   Kandivli (West)
   Mumbai - 400 067
   Maharashtra, India
   (c) Indian National

   (a) Choubey Ajit
   (b) IPCA Laboratories Limited
   Sejavta, Ratlam,
   M. P. - 457 002
   India
   (d) Indian National

Original

(1185)
1185/mum/2003
14/11/2003

Received Rs. 3000/- in Cash
from M.G.P.C. on 14/11/03
Vide Entry No. 5560 in the
Register of Valuables, Bombay

(a) **Srivastava Bimal Kumar**
(b) IPCA Laboratories Limited
Sejavta, Ratlam,
M.P. – 457 002
India
(c) Indian National

(a) **Porwal Rajendra Kumar**
(b) IPCA Laboratories Limited
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M. P.- 457 002
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(a) **Gautam Prashant**
(b) IPCA Laboratories Limited
123-AB, Kandivli Industrial Estate
Kandivli (West)
Mumbai - 400 067,
Maharashtra, India
(c) Indian National

4. That we are the assignee(s) of the true and first inventors.

5. That our address for service in India is as follows:

GOPAKUMAR NAIR ASSOCIATES, NAIR BAUG, AKURLI ROAD, KANDIVLI (EAST), MUMBAI – 400 101.

6. Following declaration was given by the inventor(s) :

We the true and first inventors for this invention in the convention country declare that the applicant(s) herein are our assignee

(Mehra Janakraj Karamchand)

(Choubey Ajit)

(Srivastava Bimal Kumar)

(Porwal Rajendra Kumar)

(Gautam Prashant)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Following are the attachment with the application:
   (a) Provisional specification (2 copies)
   (b) Statement and Undertaking on Form 3
   (c) copy Form 26 (Original Power of Attorney in our favour has been submitted with application number 150/MUM/2003)
   (d) Fee Rs.3000/- in cheque bearing No. 623917 dated 14th Nov, 2003 on Global Trust Bank Limited, Mumbai.

We request that a patent may be granted to us for the said invention.

Dated this the 14th day of Nov 2003

Dr. Gopakumar G. Nair
Agent for the Applicant
Gopakumar Nair Associates
Nair Baug, Akurli Road, Kandivli (East),
Mumbai – 400 101, Maharashtra, India

To
The Controller of Patents
The Patent Office,
At Mumbai.

FORM 2

THE PATENTS ACT, 1970

(39 of 1970)

PROVISIONAL SPECIFICATION

[See section 10]

"AN IMPROVED INDUSTRIAL PROCESS FOR MANUFACTURE OF METOPROLOL BASE AND SALTS THEREOF"

(a) **IPCA LABORATORIES LTD.**

(b) 48, Kandivli Industrial Estate, Mumbai – 400 067, Maharashtra, India

(c) Indian Company incorporated under the Companies Act 1956

The following specification describes the nature of the invention.

Duplicate

1185mum/2003

An improved industrial process for manufacture of Metoprolol base and salts thereof

Technical Field of the invention:

This invention relates to an improved industrial process for manufacture of β-blocker, antihypertensive compounds more particularly Metoprolol base and salts thereof.

Background and Prior Art

Metoprolol and its salts such as tartrate and succinate are well established drugs having anti-hypertensive activity. These compounds acts as β-blockers. The patients suffering from hypertension needs to be on treatment by these drugs for the whole lifetime. This kind of therapy necessitates that; the drugs are of high purity with very less impurity levels, so that the side effect is minimum. It also demands to produce these drugs at cheaper prices.

Ample literature is available for producing metoprolol base and its salts, due to the significance of these compounds as anti hypertensive agents.

Spanish patent ES 2011584 (equivalent US Patent 5082969) describes a process for metoprolol, where 4-(2-methoxyethyl) phenol and epichlorohydrin are reacted in aqueous alkaline conditions at 0° - 25°C temperature for 15-20 hours. The organic phase consisting of epoxide is separated, washed with water and used as such for reaction with large excess of isopropylamine in aqueous media like water at 0° - 30°C temperature.

Polish Patent PL 158497 describes a process wherein 4-(2-methoxyethyl) phenol and epichlorohydrin are reacted at 20° - 80°c temperature for 3 hours under aqueous alkaline conditions. The epoxide so formed is reacted with large excess of isopropyl amine (medium as well as reactant) to yield metoprolol base.

Nearest prior art to the present invention is the form of US Patent 6252113, discloses

reaction between 4-(2-methoxyethyl) phenol and epichlorohydrin in aqueous alkaline conditions at 50° - 70°C temperature for 1 hour. The resulting epoxide is distilled under high vacuum to improve quality. Pure epoxide then is treated with isopropylamine in solvent such as isopropyl alcohol.

As has been seen, lot of knowledge in the present filed of invention is available; however, there remain some problems, which lead the scope for further investigations. It can be seen that almost all prior art have reactants per same. Reactions which are carried out at lower temperatures (below ambient) leads to slow rate of reaction with more impurity levels when the reaction at higher temperature range is carried out, the rate of reaction increased but required purification by distillation under high vacuum.

In the processes where purification of epoxide is avoided, the resultant products are formed with higher impurities. The processes involving excess use of isopropyl amine leads to increased costs. The products formed with higher impurity levels necessitate extra purifications, which enhances the costs.

Therefore, it is of importance to develop a process for manufacture of metoprolol base, which is economical, eco-friendly and yielding high quality with higher yields, which also avoids the operations like high vacuum distillation.

The patients suffering from hypertension needs to be on treatment by these drugs for the whole lifetime. This kind of therapy necessitates that; the drugs are of high purity with very less impurity levels, so that the side effects are minimum. It also demands to produce these drugs at cheaper prices.

Objectives:

The objective of the present invention is to develop a process for manufacture of Metoprolol base and salts thereof, in high yields with higher purity and better operator friendly operations at cheaper prices.

Summary of the Invention:

This invention relates to an improved industrial process for manufacture of β-blocker, antihypertensive compounds more particularly Metoprolol base and salts thereof.

Detailed Description:

The present invention has been made possible to produce metoprolol base and its salts in higher yields with high purity and avoiding processes like high vacuum distillation, at cheaper costs.

The present invention involves optimization of reaction temperatures, molar ratio of reactants in order to achieve higher purity and yields by avoiding purification of epoxide intermediates.

The present invention process involves three steps. In the first step is for preparation of epoxide by reacting 4-(2-methoxyethyl) phenol with epichlorohydrin in an aqueous media containing inorganic base such as sodium hydroxide at 40-45°C temperature.

The resultant epoxide is used in the second step for preparation of metoprolol base. The epoxide is treated with isoproplyamine in aqueous media to obtain Metoprolol base of high purity in high yields. The last step is converting metoprolol base into the succinate and tartrate salts by reacting with acids like succinic acid or tartaric acid in solvent media such as acetone by any conventional method.

By following the present invention as described below, it has been made possible to produce metoprolol base and its salts in higher yields with high purity and avoiding processes like high vacuum distillation, at cheaper costs.

The present invention involves optimization of reaction temperatures, molar ratio of reactants in order to achieve higher purity and yields by avoiding purification of epoxide intermediates.

EXPERIMENTAL

It involves three steps :

Step- I : Epoxide formation by reacting 2-(methoxyethyl) phenol with epichlorohydrin.
Step-2 : Metoprolol base from reaction of epoxide with isopropyl amine.
Step- 3 : Metoprolol salts from metoprolol base

The process of the present invention is illustrated by the following example.

Step- I : Epoxide formation :

4-(2-methoxyethyl) phenol and epichlorohydrin are reacted in aqueous media like water, in presence of inorganic base such as sodium hydroxide, at temperature range of 40° - 45°C in 3 to 5 hours time.
The molar ratio of 4-(2-methoxyethyl) phenol to epichlorohydrin used in the range of 1 : 0.92 to 1 : 2.0, wherein the more preferred ratio is 1 : 1.1 to 1 : 1.4 and the most preferred ratio is 1 : 1.31.
Most preferred concentration of sodium hydroxide in water is 25% w/v
Preferred molar ratio of sodium hydroxide to 4-(2-methoxyethyl) phenol used is 1.14 : 0.95, more preferred is 1.024 : 1 and the most preferred ratio is 1.136 : 1
Reaction is carried out in the temperature range of 10° to 45°C, where in most preferred is 40° to 45°C.
Most preferred ratio of 4-(2-methoxyethyl) phenol : water is 1 : 1.6 volumes.
At the end of reaction, aqueous and organic phases are separated out.
The organic phase is washed thrice by water. The pH of washing must be in the range of 7 to 8. This pH range is necessary to achieve high purity of the epoxide.

Traces of water are removed from organic phase by azeotropic distillation under vacuum below 55°C temperature. Keep the residue at 55°C, under vacuum for 3 to 5 hours, till the purity of sample is achieved in the range of 96-98%

The yield of the epoxide, so obtained is in the range of 93-95% of stoicheometric and purity 97-99%.

The epoxide with above purity is used for making metoprolol base.

Step-2 : Metoprolol base

The epoxide and isopropyl amine are reacted in aqueous media like water at temperature 0° - 30°C.

Preferred temperature during addition of epoxide is 10° to 25°C, while the most preferred temperature for completion of reaction is 30°C

Reaction completes in 3 hours time at 30°C.

Preferred molar ratio of epoxide : isopropyl amine is 1 : 5.0 – 5.5 where in the most preferred ratio is 1 : 5.2 - 5.3

Ratio of water to epoxide is 2 : 1 vol. : wt.

On completion of reaction, the reaction mixture is cooled to 0° – 5°C.

In order to achieve high purity it is necessary to maintain above temperature range. Formation of impurity at RRT 0.35 (By GC) is minimized by operating at 0° - 5°C. It is observed that in cases temperature rises above the range, this impurity increases.

The reaction mass is quenched by 2.25 volume of water. The product is extracted by 3 volumes of toluene. The toluene layer is washed three times by water for removal of isopropyl amine content is less than 0.5%.

Traces of isopropyl amine are removed by maintaining under vacuum below temperatures 25° C. It is necessary to eliminate traces of isopropyl amine at low temperature below 25° C, as the presence of isopropyl amine during distillation of toluene above 25° C leads to the formation of an impurity at RRT 1.54 by (GC). Following the present invention process this impurity formation is avoided.

In case when isopropyl amine remained in the traces, the impurity at RRT 1.54 (by GC) is detected.

Thus, following process as per present invention, formation of the impurities at RRT 0.35 & RRT 1.54 are under control, which leads to yield highly pure Metoprolol base in higher yields.

The analysis of sample of toluene layer shows absence of isopropyl amine. Toluene is distilled out at temperature 30° - 40°C under vacuum.

The residue of metoprolol base so obtained shows purity more than 99% and the yield of which is in range of 88 to 89%. (Stoicheometric)

Step- 3 : Metoprolol salts from metoprolol base

Metoprolol succinate :

The metoprolol base is dissolved in seven volumes of acetone and carbon treatment done at 45°C. Solution of Succinic acid in stoicheometric proportion to Metoprolol base i.e.1:2 is prepared in twenty volumes of acetone by refluxing. Succinic acid solution is added to metoprolol base solution and adjusted pH 7.1-7.3. Reflux the reaction mixture for 4-5 hours and is cool to 26° C. Maintain the same temperature of the reaction mixture with stirring for two hours and is filtered. The Metoprolol succinate salt obtained is purified by crystallization from three volume of methanol. The resultant Metoprolol succinate obtained in yield of 72-75 % (Stoicheometric) with purity more than 99.8% by HPLC and any other impurity less than 0.1%.

Metoprolol tartarate :

The metoprolol base from the above step is dissolved in seven volumes of acetone and added activated charcoal, heat to 45°C., stir for 30 minutes and filter the charcoal. Solution of tartaric acid in acetone is prepared by dissolving tartaric acid in stoicheometric proportion of 1:2 (Metoprolol base) in 18 volumes of acetone by refluxing. The tartaric acid solution is added to Metoprolol base solution under refluxing condition and adjusted pH 6.1-6.3. The reaction mixture is refluxed for 4 hours and cool

to 26°C. Reaction mixture is stirred at 26°C for 2 hours and filter. The yield of Metoprolol tartrate obtained is 83-83% (Stoicheometric).

The Metoprolol tartarate is then crystallized from nine volumes of isopropyl alcohol.

The pure Metoprolol tartarate obtained in 72-73 % yield (stoicheometry) with purity >99.8% by HPLC and any other impurity NMT 0.1%.

Dated this the 14th Day of Nov 2003

Dr. Gopakumar G. Nair

Agent for the Applicant